

# **CARBAMAZEPINE-IBUPROFEN CO-CRYSTAL SCREENING USING NON-STOICHIOMETRIC METHOD**

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## ABSTRACT

Co-crystals is a facilitating technology that is used in new or existing drug delivery systems by majority of pharmaceutical companies in formulation of drug development. However the challenging aspects in development of drug molecules are correlated with their slow dissolution in biological fluids and thus insufficient and inconsistent systemic exposure, and consequent sub-optimal clinical effectiveness. The traditional approaches to deal with the issues of poor aqueous solubility often fail to create a viable solid form which is insufficient to provide enough enhancement of bioavailability. And so, there is enormous potential to explore co-crystal design of marketed APIs among each other to enhance the solubility and bioavailability of the product. This paper presents the co-crystal screening approach through the study of carbamazepine (CBZ) and ibuprofen (IBU). The screening was conducted using non-stoichiometric methods (solid addition of CBZ to saturated solution of IBU). In the experiment, CBZ-IBU co-crystal was prepared in various solvents and left to equilibrate in three conditions; stagnant, manually agitated and shaken in three days to produce the co-crystal. Physical characterization of the solid co-crystal is being characterized by using optical microscopy for its morphology as well by using differential scanning calorimetry (DSC) to determine the thermal properties. The only co-crystal of CBZ-IBU success to form using the non-stoichiometric approach is in formic acid solvent whereas for the others, they behaving more likely to be CBZ in different forms. Overall, DSC analysis shows that either CBZ or IBU occurred due to the peak which corresponded to their melting point. From this study, it can be concluded that co-crystal formation between CBZ-IBU using non-stoichiometric method only successful in formic acid.

## ABSTRAK

Ko- kristal adalah teknologi mudah yang digunakan dalam sistem penyampaian ubat baru atau sedia ada oleh majoriti syarikat-syarikat farmaseutikal dalam formulasi ubat-ubatan. Walau bagaimanapun, aspek mencabar dalam formulasi ubat-ubatan berkait rapat dengan kadar disolusi yang perlahan dalam cecair biologi yang secara tidak langsung menyebabkan pendedahan yang tidak cukup dan konsisten seterusnya memberi kesan kepada keberkesanan sub-optimum klinikal. Pendekatan tradisional yang digunakan untuk menangani isu-isu berkenaan dengan kelemahan larutan akueus seringkali gagal untuk mereka bentuk pepejal yang bertepatan untuk meningkatkan bioavailabiliti. Oleh itu, terdapat potensi yang besar untuk meneroka reka bentuk bersama ko-kristal antara API dan API yang dipasarkan untuk meningkatkan tahap kelarutan dan bioavailabiliti produk. Kertas kerja ini mengkaji ujikaji saringan pembentukan ko-kristal antara carbamazepine (CBZ) dan ibuprofen (IBU). Pemeriksaan pembentukan co-kristal telah dijalankan menggunakan kaedah tidak stoikiometri (penambahan pepejal CBZ kepada larutan tepu IBU). Dalam eksperimen ini, ko-kristal CBZ - IBU telah disediakan dalam pelbagai pelarut dan dibiarkan dalam tiga keadaan; bertakung, dikacau secara manual dan digoncang dalam tiga hari untuk menghasilkan ko-kristal. Analisis terhadap sifat fizikal pepejal co-kristal menggunakan mikroskop optik untuk memeriksa morfologi ko-kristal dan sifat-sifat thermal dianalisis menggunakan pengimbasan kolimetri (DSC). Satu-satunya ko-kristal CBZ – IBU yang berjaya terbentuk menggunakan teknik bukan stoikiometri adalah dalam larutan asid formik manakala bagi yang lain, mereka lebih cenderung untuk menjadi CBZ dalam bentuk yang berbeza. Secara keseluruhannya, analisis DSC menunjukkan bahawa sama ada CBZ atau IBU berdasarkan titik leburnya. Dari kajian ini, kesimpulan yang boleh dibuat ialah pembentukan ko-kristal antara CBZ - IBU hanya berjaya dalam asid formik.

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## LIST OF ABBREVIATIONS

4-ABA	4-Aminobenzoic acid
API	Active pharmaceutical ingredient
BCS	Biopharmaceutical classification system
CBZ	Carbamazepine
CBZ (D)	Carbamazepine dihydrate
CCF	Co-crystal former
CSD	Cambridge structural data
DRH	Deliquescent relative humidity
DSC	Differential scanning calorimetry
FTIR	Fourier transforms infrared
H	Hydrogen
HPLC	High-performance liquid chromatography
IBU	Ibuprofen
IP	Intellectual property
N	Nitrogen
NCT	Nicotinamide
NSAID	Non-steroidal anti-inflammatory drugs
O	Oxygen
RC	Reaction co-crystallization
RH	Relative humidity
SAC	Saccharin
SEM	Scanning electron microscopy
TGA	Thermalgravimetry analysis
TPD	Tertiary phase diagram
XRD	X-ray diffraction
XRPD	X-ray powder diffraction



# 1 INTRODUCTION

## *1.1 Motivation and statement problem*

Pharmaceutical industry developed major resources in identifying novel active pharmaceutical ingredients (APIs) with suitable physiological profiles that formulated into drugs. However, the development of drug molecules is quite since it often correlated with their slow dissolution in biological fluids that will lead to insufficient as well as inconsistent systemic exposure, and consequent sub-optimal clinical effectiveness. The traditional approaches such as solid dispersions and salt formation, used to overcome these issues often fail in order to generate a viable solid form as the increase in dissolution rate; however it is insufficient to provide enough enhancement of bioavailability. In addition, all these techniques are costly and quite complex, and are only applicable for some types of drugs.

Most of APIs are developed and marketed orally as solid dosage forms that contain a defined crystalline form of an API. Hence, co-crystallization of API is now recognized as a facilitating technology that is used in new or existing drug delivery systems by majority of pharmaceutical companies in providing a route to dramatically influence material properties. And so, there is enormous potential to explore co-crystal design of marketed APIs among each other to enhance the solubility and bioavailability of the product (Zaworotko, 2006; Schultheiss et al. 2009). Yet, relatively less is known about the strategic design principles that could lead to the modification or improvements of their physical and chemical properties.

It has been reported that co-crystal can be screened using various methods. Co-crystal screening technology has the ability to discover, as well as establish new intellectual property (IP) for new drug-drug co-crystals of multiple APIs to protect the product from competition. Development of co-crystal screening may lead to commercialization of new co-crystal product along with separated single enantiomers. A patent of a drug-drug co-crystal in the case of API-API combination with enhanced drug properties than previously known forms could be of high commercial value in market. Designing drug-drug co-crystals may shorten the development time (including clinical trials) than those

of new chemical entities as co-crystals do not engage structural modification of the APIs (Shekon, 2012). Nevertheless, most of the previous co-crystal studies using stoichiometric method such as evaporation and wet grinding techniques, it is of great interest to evaluate the screening approach for co-crystal using non-stoichiometric method. Despite of researcher's interest for multi-API co-crystal study, there still no study of co-crystal between carbamazepine (CBZ) and ibuprofen (IBU) drugs. Therefore, the presents works aim to propose the experimental studies of co-crystal formation of CBZ-IBU using non-stoichiometric screening method.

## ***1.2 Objectives***

The objective of this research is:

- To access the co-crystal formation of CBZ-IBU using non-stoichiometric screening method.

## ***1.3 Research scope***

The following are the scope of this research:

- i) Prepare the saturated solution of co-crystal former (CCF) in different solvents namely acetonitrile, ethanol, ethyl acetate, propanol, and formic acid.
- ii) Co-crystal screening using non-stoichiometric method in three conditions which are stagnant, continuous shaking and manually agitated.
- iii) Co-crystal characterization using:
  - a) Differential Scanning Calorimetry
  - b) Optical microscopy

## ***1.4 Work contribution***

The value of co-crystals with pharmaceutical components lies in the ability to alter the functionality of the materials. Pharmaceutical researchers often consider alternative solid state forms to a free drug compound, such as polymorphs or salts, in order to improve pharmaceutical properties. However, some compounds without a suitable ionisable site (basic or acidic) for proton transfer, will have to eliminate salts formation as an option for drug formulation.

Thus, co-crystals which involve no proton transfer could become practical alternative in drug formulation for this type of compound. Properties relates to drug performance and that can be controlled by co-crystal formation include melting point, chemical stability, dissolution rate, bioavailability, solubility, as well as mechanical properties.

Hence, the findings of this project will lead to the potential use of drug-drug co-crystals in industrial drug formulations. The fundamental and mechanisms behind the co-crystal formation must be fully understood, hence will attracted on the industrial interest into this area of studies, providing direct benefits to the pharmaceutical field and wider long term benefits to public health.

## ***1.5 Thesis organisation***

The structure of the thesis is outline as follow:

Chapter 1 discuss on motivation and problem statement lead to this study. The objective and research scopes and work contribution also include in this chapter.

Chapter 2 provides a description on co-crystal design, focused on the intermolecular interactions theory that later will lead to the development of supermolecules. A general description on selection of co-crystal former, as well as the co-crystal properties and mechanism which co-crystal formation can enhance solubility are presented. This chapter also provides a brief discussion of the co-crystal screening techniques available and the co-crystal characterization. A summary of the previous experimental work on carbamazepine co-crystal is also presented.

Chapter 3 gives a review of the screening approach applied for co-crystal formation using non-stoichiometric method including the type of solvent used, and solution procedures through solid addition to saturated solution of CCF with selected solvents. The product crystals obtained were characterized using differential scanning calorimetry (DSC) in order to check on crystal's melting point and optical microscopy for it morphology.

Chapter 4 is devoted to a result and discussion where experimental data obtained using DSC characterization and optical morphology of crystal product presented. Result for confirmation of co-crystal formation analyzed using both of characterization technique compared against different solvent used. A detailed description in different melting point as well as morphology also outlined and compared with result obtained from previous studies.

Chapter 5 represents the summary of the work presented in this thesis and identified areas that can benefit from further research.

## 2 LITERATURE REVIEW

### 2.1 Overview

This chapter introduced co-crystals design, including the criteria for selecting co-crystal formers based on the synthon theory. The next section will focus on the pharmaceutical properties that can be altered by co-crystal approach for an API, including the stability, bioavailability, dissolution rate as well as mechanism of co-crystal which enhance solubility. The screening method i.e. solution and solid-state approaches in designing co-crystals and understanding the kinetics and mechanisms behind co-crystallization were discussed. Some of the characterization techniques used in co-crystal studies were as well discussed. The final two sections are devoted to the model compounds used in this experimental study which are CBZ and IBU. Final section discussed on several case studies from previous work of CBZ co-crystals formation.

### 2.2 Introduction

Co-crystals is crystalline structure consists of two or more neutral or organic components and solid in ambient conditions in their pure form. The intermolecular interaction occurred in co-crystal including hydrogen bonds, van der Waals, and  $\pi$ - $\pi$  stacking and the most favourable geometry will lead to a supramolecular network. The co-crystals formation has an advantages of forming viable solid forms of APIs co-crystal even though without possess any ionisable functional groups and is believed to have better improvement in their pharmaceutical properties which unavailable in single component of API solid phases either in polymorphs or amorphous forms. Pharmaceutical co-crystal consists of an API together with a co-crystal former (CCF) which usually exists in the neutral state and mostly interact by hydrogen bonding. Tendency of hydrogen bonding interaction between various functional groups on API is often considered as a significant factor to a successful co-crystal formation (Childs et al., 2007; Reddy et al., 2009).

Pharmaceutical co-crystal's design that has multiple molecular components is important to control pharmaceutical properties without changing the molecular interaction. Lots of studies have been conducted, however, at determining new co-crystal form with different packing motif with no direct a priori ability to logically and reliable target

specific on physical properties of the pharmaceutical agents. Despite the fact that most studies discover new pharmaceutical co-crystal forms and their associated crystal structures, few addresses the strategic design principles that could possibly lead to the modification or enhancement of their physical and chemical properties. Therefore, design of co-crystals believed to enhance the variety of solid state forms of an API even for non-ionisable APIs, and improve their properties by alteration of solubility, dissolution rate, chemical stability, bioavailability and mechanical properties (Remenar et al., 2003; Rodríguez-Spong et al., 2003; Childs et al., 2004; Rodríguez-Spong et al., 2004; Zocharski et al., 2004; Trask et al., 2005; Nehm et al., 2006). Families of API co-crystals are being designed by considering the thermodynamic, molecular recognition, as well the kinetic theories to assemble hydrogen-bonded molecular of multiple components.

### 2.3 Co-crystal design

The intermolecular interactions understanding focused in crystal engineering lead to the development of supermolecules. The hydrogen bond has been the most important interaction in co-crystal formation due to its strength and directionality (Etter, 1990; Etter et al., 1991; Desiraju, 2002; Wenger et al., 2008). Important knowledge is gained to identify hydrogen-bond preferences and reliable synthons that lead to co-crystal formation by studying these hydrogen bond designs (Leiserowitz et al., 1969; Etter, 1990; Desiraju, 1995; Aakeroy et al., 2002; Wenger et al., 2008). Cambridge Structural Database (CSD) can be used to study on the occurrence of hydrogen bond motifs and other main interactions in crystal lattices based on the specific molecules, functional groups, and their synthons (Etter et al., 1991; Nangia et al., 1998; Allen, 2002). Some generally found synthons are shown in Figure 2.1.

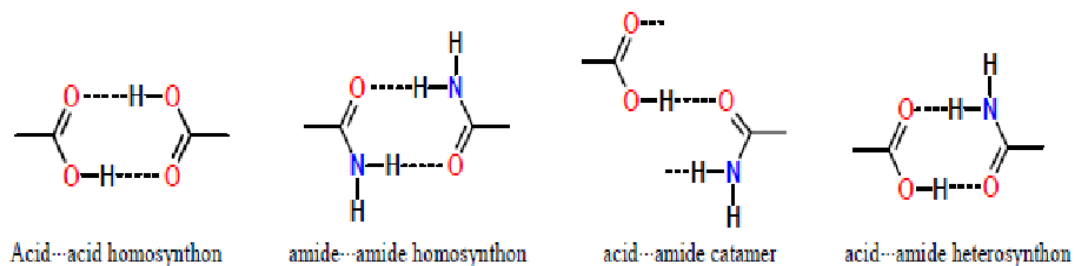


Figure 2-1: Common synthons found between carboxylic acid and amide functional groups. (Etter, 1991)

Parameters for preferred hydrogen bond patterns in crystals based on rigorous analysis of hydrogen bonds and packing motifs have been developed by Donohue in 1952 and Etter in 1991. These includes: (a) there are hydrogen bonding with the crystal structure of that compound for all hydrogen existing in molecule (Donohue 1952), (b) if there are available hydrogen-bond donors, each of good acceptors will be used in hydrogen bonding (Etter, 1991), and (c) the best hydrogen-bond acceptor and the best hydrogen-bond donor will preferentially form hydrogen bonds to one another (Etter 1991). Etter also studied on numerous of reasons at which this behaviour impossible to occur. These include the existences of multiple competitive hydrogen-bond sites, steric hindrances, or competing dipolar or ionic forces and conformational freedom. These common principles however create the basic for predicting for likely and unlikely structures. These principles of co-crystal formation were applied to carbamazepine (CBZ), an API which has the reliable carboxamide synthon.

CBZ of interest because it has low water solubility and it's well known four anhydrous polymorphs design and also exists as a dihydrate when exposed to moisture (Himes et al., 1981; Reboul et al., 1981; Lowes, Caira et al., 1987; Murphy et al., 2002; Grzesiak et al., 2003) and solvates (water and acetone solvates) (Terrence et al., 1983; McMahon et al., 1996; Kobayashi et al., 2000; Fleischman et al., 2003). The crystal packing of CBZ in different forms of polymorphs and solvates explains the design of cyclic dimer, with the carboxamide group act as both of hydrogen bond acceptor and donor.

Examination of the crystal structures of solvates reveals hydrogen-bonding arrangements that can be applied to co-crystal formation. In many solvates, the solvent molecule is hydrogen-bonded to the API molecule. In case of CBZ, these solvates of CBZ confirm that the tendency of an API molecule exist as solvates is resulted from the molecular structures, hydrogen bond patterns, and crystal packing (Khankari et al., 1995; Nangia et al., 1998; Bingham et al., 2001; Infantes et al., 2002; Gillon et al., 2003). Supramolecular design strategies were utilized to prepare CBZ co-crystals using principle of the primary supramolecular synthon where molecular interactions either retain (strategy I) or disrupt the carboxamide dimer formation (strategy II) (Fleischman, Kuduva et al. 2003). Strategy I maintain the carboxamide homosynthon and uses of the external hydrogen bond donor and acceptor sites. While strategy II forms a heterodimer between the carboxamide and carboxylic groups by hydrogen bonds.

## ***2.4 Co-crystal former selection***

Selection of co-crystal former is most commonly based on the synthon theory (Desiraju, 1995) which builds within the co-crystal a supermolecules by consuming specific molecular fragments to create supramolecular synthons. The synthon theory proposes that for each functional groups present on the API and the co-crystal former will play a vital role for successful formation of co-crystals.

Although formation of the supermolecule may be favourable for supermolecule itself to be able pack into an ordered crystalline structure, however the disadvantage of the synthon theory is that it is not quantitative in so far. Additionally, other factors such as competition among the different functional groups present in API or the co-crystal former nor the steric density around the donor and acceptor does not considered in this theory. A study by Fabian and Fayos suggested that co-crystal formers selection based on shape and polarity would influence the success of co-crystal formation (Fabian, 2009; Fayos, 2009). On the other hands, Musemeci et al., in 2011 and Issa et al., in 2009 have proposed computational approaches in predicting the results of co-crystallization formation and Galek et al., in 2007 have developed a knowledge-based method for predicting the result of various co-crystallization reactions that may occur during the process.

The approach has been later used by Delori et al. for further research of the anti-malarial drug pyrimethamine (Delori et al., 2012; Delori et al., 2013). Abramov stated that, the influence of fluid-phase thermodynamics can be used for efficient and accurate screening technique of co-crystal formers for the co-crystallization of API. This finding is based on the comparison between excess enthalpy of an API and co-crystal former mixture virtual to the pure components (Abramov et al., 2012).

## ***2.5 Co-crystal properties***

Examples in the preceding section show that co-crystallization changes the interactions as well the composition of pharmaceutical materials. As such one can expect changes in physico-chemical properties such as chemical stability, melting points, hydrate formation, dissolution rates, bioavailability and solubility due to co-crystallization of pharmaceutical materials. This has been demonstrated for a few API co-crystals.



### 2.5.1 Chemical stability

Co-crystallization can improve the chemical stability of an API. For instance, carbamazepine is reported to undergo chemical degradation to cyclobutyl dimer after forming a hydrate (Matsuda et al., 1994; Rodriguez-Spong, 2005). The degradation reaction requires that the distance between the azepine rings of adjacent CBZ molecules be less than or equal to 4.1 Å (Rodriguez-Spong, 2005). Co-crystallization of CBZ with co-crystal formers such as saccharin (SAC) or nicotinamide (NCT) alters the molecular interactions and packing arrangement of CBZ molecules. Hence, these co-crystals exhibit greater stability against hydration and degradation.

### 2.5.2 Melting points

It is a normal practice to check on the melting point of a compound for the characterization or purity identification; but, within pharmaceutical sciences, the determination on melting point is very important due to its relationships to aqueous solubility and vapour pressure (Abramowitz et al., 1990). In fact, the melting point has also been correlate to the Log of solubility, although assumptions on the entropy of fusion had to be drawn (Jain et al., 2001). Thus, in order to alter its aqueous solubility toward any particular purpose, being able to determine the melting point of a selected API before it was synthesized would be very beneficial. However, correlations relating chemical structure to melting point data remain indefinite. Factors contributing to the melting point of a crystal product such as the molecular arrangement within the crystal lattice, intermolecular interaction, molecular symmetry, and conformational degrees of freedom for a molecule, one clearly face the difficulties in trying to describe comparisons between molecular structure and crystalline lattice energy relate to the melting point. This situation becomes more complex when determining the multi-component's melting point because each of the components has its own characteristic properties and can influence the environment and intermolecular interactions around it (Katritzky et al., 1995). In addition, co-crystals with lower melting points can be advantageous during pharmaceutical processing, for instance when a melted state of a thermally labile API is needed during some processes such as hot melt extrusion, a co-crystal with a lower melting point than pure crystalline API will allow for melting at lower temperatures to avoid chemical degradation neighbours.

### **2.5.3 Hydrate formation**

APIs can be co-crystallized with co-crystal formers such that the API will not form a hydrate or a solvate. Since co-crystals are supramolecular assemblies and are designed based on functional groups and hydrogen bond complementarity, solvate formation that rely on this complementarity will be inhibited by the formation of co-crystals, given that the intermolecular interactions between the API and co-crystal former are stronger than between the solvent molecule and API. An example of this study is on the stability of CBZ co-crystals with nicotinamide (NCT) or saccharin (SAC) when exposed to high relative humidity (Rodríguez-Spong & Zocharski et al. 2003; Rodríguez-Spong 2005). Even though the pure CBZ anhydrous crystal transforms to carbamazepine dihydrate when exposed to high relative humidity, the co-crystals do not (Rodríguez-Spong 2005). A similar study on caffeine shows that the caffeine-oxalic acid co-crystal did not transform to caffeine hydrate under high relative humidity for seven weeks. However, other caffeine co-crystals dissociated and consequently, the hydrated form of the API resulted (Trask, Motherwell et al. 2005).

### **2.5.4 Dissolution Rate**

Dissolution rate of different API co-crystal have been reported. The intrinsic dissolution rates of CBZ-SAC co-crystal in water are 1.7 and 2.3 times that of pure CBZ and close to the single component of anhydrous CBZ form III (Rodríguez-Spong, 2005). Childs et al formulated crystalline complexes with a salt form of an API and carboxylic acids. For example from previous work, fluoxetine hydrochloride, antidepressant drugs was crystallized with benzoic acid, succinic acid, and fumaric acid where the chloride ion acts as a hydrogen bond acceptor for carboxylic acid groups of the three ligands. Intrinsic dissolution studies were conducted at 10°C because at 25°C, the rates were so rapid that the dissolution rates of the co-crystal could not be distinguished from one another (Childs et al., 2007).

### **2.5.5 Bioavailability**

Bioavailability studies need to be carried out if co-crystal were going to be a practical alternative for solid state forms of a drug. Bioavailability studies revealed the co-crystal achieved approximately three higher plasma concentrations for the same dose in dog (Mcnamara et al., 2006). Research of CBZ-SAC was reported to yield slightly higher

plasma levels when compared to dosing CBZ monoclinic, although the authors reported that the increase was not statistically significant (Hickey et al., 2006).

### **2.5.6 Mechanism by which co-crystal enhance the solubility**

The strength of the crystal lattice and the solvation of co-crystal components are two independent factors that determine the solubility. One can lower the lattice energy or increase the solvent affinity in order to increase the solubility. Co-crystals capable to influence both factors to different extent (Serajuddin, 2007; Anderson et al., 1985). The solubility in solvents being controlled by the crystal lattice where there have little resistance to solvation, or when solvent–solute interactions match the solvent–solvent interactions, as in ideal solutions. In contrast, solvation will play an important role on the solubility of co-crystals as a result from the drug hydrophobicity (Liu, 2008; Yalkowsky, 1999).

Majority of hydrophobic drug co-crystals show this performance as the limitations imposed by the solvent–solute interactions (hydrophobicity) had reduced the solubility below that the determined by lattice energy (Maheshwari et al., 2012; Alalaweh et al., 2012). The solvation and lattice contributions to the solubility of carbamazepine co-crystals in organic and aqueous solvents (Gao et al., 2011; Good & Rodriguez-Hornedo, 2010) were based on the graphical method developed by Miyako and co-workers (Miyako et al., 2008). The solubility lowered by solvation by as much as an order of magnitude in organic solvents and orders of magnitude in water. In fact, solvation like hydrophobicity of the solute limited the melting point to be often poor parameter to determine aqueous solubility of co-crystals and not influence by the lattice energy (Gao et al., 2011; Bak et al., 2008).

The degree of the solvent–solute interaction in organic solvent is often proportional to the magnitude of the lattice strength, and thus enhance in co-crystal solubility are related with the decreases in melting point. However the situation is quite different in water where the solvation (hydrophobicity) limits the solubility to a larger extent than lattice strength and the magnitude of each factor is not proportional. Consequently, melting point will be a poor parameter of aqueous solubility for these co-crystals. Co-crystal solubility has also been influenced with co-crystal former solubility Childs et al., 2008; Gao et al., 2011). Decrease in the solvation barrier for a co-crystal to an extent

proportional to that of the pure co-crystal former resulted from the solubility behavior. While universal parameters of co-crystal solubility would be helpful, each case still needs a careful analysis on the factors that correlated with solubility.

## ***2.6 Co-crystal screening***

Throughout the co-crystalline literatures, numerous solution-based and solid-based mediated techniques have been used to screen the co-crystals. Current findings in solution-based technique to screen co-crystals include slow evaporation (Caira 1991; Etter et al., 1991; Ghosh et al., 1991; Fleischman et al., 2003; Walsh et al., 2003; Childs et al., 2004) from solutions with stoichiometric or equimolar concentrations of co-crystal components and solvo-thermal methods (Bettinetti & Caira et al. 2000; Rodríguez-Spong 2005), with the co-crystal former being more common. However all these processes suffer the risk of crystallizing the only single component phases, thus decreasing the opportunity to form the multiple component crystalline phases. Consequently, from these practically based approaches, numerous of experimental techniques are often tested and ability to larger the scale co-crystallization processes is limited (Morissette et al., 2004).

Co-crystallization product can occur during storage of solid mixtures of co-crystal components and solvent additive (Jayasankar et al. 2007). Co-crystallization in these solid co-crystal and solvent additive mixtures is assisted by moisture sorbed due to deliquescence of solvent additive at relative humidity above the deliquescent relative humidity (DRH). It is assumed that the water absorbed by the deliquescent material generates a medium for the co-crystal products to dissolve. The rate of co-crystal formation depends on the rates of moisture sorption, dissolution of co-crystal components and rate of nucleation as well as growth from solution phase.

Co-crystal formation in the solid state method is based on mechanical activation of materials by processes such as dry grinding or milling and studies done for these processes of co-crystal are abundant (Etter, 1990; Etter, 1991; Etter et al., 1991; Etter et al., 1993; Caira et al., 1995; Pedireddi et al., 1996; Oguchi et al., 2000; Trask et al., 2005; Trask et al., 2005; Jayasankar et al., 2006; Childs et al., 2008). Adding up of few drops of solvent in co-crystal grinding technique is becoming increasingly common (Trask et al., 2004; Wenger et al., 2008). Since grinding technique is quite highly

energetic process, co-crystal formation by co-grinding reactants with few drops of solvent continues throughout the development of amorphous phases of the reactants. This has been proven in studies by Jayasankar et al. using anhydrous form III CBZ and SAC (Jayasankar et al., 2006). Faster rate of co-crystal formation was observed during co-grinding at room temperature. Interestingly, CBZ-NCT and CBZ-SAC co-crystal were shown to spontaneously formed under a variety of storage conditions even when the two components were not grind together; suggesting that transformation from single components to multi-components was thermodynamically favourable (Maheshwari et al., 2009). However, most of these methods though simple to be apply within the laboratory scale, was not favourable when implemented to a bigger process scale used in industrial field.

Despite significant current studies in this pharmaceutical co-crystal study, there have been few experimental studies on the effectiveness of co-crystal screening approaches using both stoichiometric and non-stoichiometric method. The non-stoichiometric method, also known as reaction crystallization method categorized in solution based crystallization where saturated or nearly supersaturated solution of CCF in a solvent with high CCF solubility has been used as a crystallization medium. Solubility difference between the co-crystal and the selected pharmaceutical drug optimized by these conditions and hence allow for the creation and maintenance of a high activity for the co-former throughout the experiment.

Theoretically, the formation of single component crystals may exist if co-crystal components A and B have non-equivalent solubility solution co-crystallisation through evaporation of an equimolar solution due to supersaturation solution of CCF is generated with respect to less soluble reactant or both less soluble reactant and co-crystal. The reaction co-crystallisation (RC) technique has been accepted for this situation. RC technique are carry out by adding reactant B to a saturated or nearly supersaturated solution of reactant A and then the solution become supersaturated with respect to co-crystal AB, where co-crystallisation then can occur:



This technique is more efficient with non-stoichiometric solution concentrations and when solutions are saturated or nearly supersaturated with respect to reactants. In one of previous study, RC technique were carry out by adding CBZ to saturated or 18 nearly saturated solutions of co-crystal formers separately and several pure CBZ co-crystals were obtained (Childs et al., 2008).

### **2.6.1 *Others screening method***

Pharmaceutical co-crystals can also be formed by technique of supercritical fluids. Supercritical fluids play new role in screening of co-crystals. Supercritical fluid technology proposes a new screening development that allows a single-step generation of particles that are impossible or difficult to obtain by traditional techniques like salt formation especially for substances with thermal sensitivity or structure instability properties. The formation of pure and new co-crystals which is crystalline molecular complexes consist of an API and one or more conformers in single crystal lattice can be obtained due to distinctive properties of super critical fluids by using different supercritical fluid properties respectively (Padrela et al., 2009).

Another solution based method which has recently attracted much more interest for potential to scale up the co-crystal production is cooling crystallisation technique which involves difference in the temperature of the co-crystallisation system. Initially, very large quantities of reactants and solvent are mixed together in a reactor usually a jacketed vessel reactor, and then the system was heated to a higher temperature in order to make sure all solutes are totally dissolved in the solvent and then followed by a cooling down process. Hence, co-crystals will precipitate once the solution becomes supersaturated with respect to co-crystal as the temperature decreased (Mcnamara et al., 2006). For example, experiment of co-crystals between caffeine and p-hydroxybenzoic acid was screen through this cooling crystallization technique (He et al., 2010). The intermolecular interactions of caffeine and p-hydroxybenzoic acid in methanol solvent at different concentration ratios have been checked by cooling crystallisation, displaying that the effectiveness on co-crystal screening not only improved by understanding the details of the intermolecular interactions only but also provides a qualitative and predictive parameter for the final crystal products.

The cooling crystallisation technique can be also applied in combination with the tertiary phase diagrams (TPDs) in describing the regions of thermodynamic stability especially in a multi-component co-crystal system and in predicting for the possibility of co-crystals formation. In other research, cooling crystallisation on concentrated solution of CBZ-NCT slurry was observed by using an in situ FTIR spectroscopy probe, in which the development of the CBZ and NCT concentration solution explained the kinetic pathways of the co-crystallisation process giving useful information on nucleation and growth of the co-crystals as well on the proportion of each solid phase present in suspension. It is possible to determine the optimal operating conditions for a cooling co-crystallisation process through only analyzing the kinetic pathways and supersaturation levels of the components (Gagniere et al., 2009).

The hot stage microscopy technique has similar advantages to grinding over the solution based methods, which are the results are rapidly obtainable, the method avoids the formation of undesired products and is considered environmentally friendly. Yet its use is often limited to co-crystal formers with comparable melting points, to avoid molecular decomposition of one co-crystal former before the other has melted.

This method is based on the contact or mixed fusion approach (Kofler, 1980; McCrone, 1987), which involves the melting process of one co-crystal former (the one with the higher melting point) between two microscope slides, which is then allowed to solidify. Second conformer was introduced between the same microscope slides and allowed to melt, consequently dissolving a proportion of the first co-crystal former at the region where they meet. This region is known as the zone of mixing. The system is next cooled down to room temperature and fully solidified, before being heated up again until all the components melt. This is observed using a microscope with crossed Polaroid filters. If co-crystallization is formed, a distinct new morphology with a different melting point to its components would be identified within the zone of mixing.

## ***2.7 Characterization of co-crystal***

Characterization of co-crystals is importance and there are different characterization methods starting from simple melting point determination to the complete structural determination through single crystal X-ray crystallography motif. Other analyzes such

as studying on the morphology of crystals by optical microscopic, observing changes in outer appearance of crystal forms.

DSC has recently been shown to be an efficient thermal method to synthesize co-crystals in situ (Lu, Rodríguez-Hornedo et al. 2008). In DSC, graph of heat flow versus temperature must be obtained where the heat flow to the sample must increase dramatically according to the setting temperature in order for the sample to melt completely and use the same heating rate for reference pan. Theoretically, if the heating curves showed two distinct melting peaks over the complete composition range, indicating that these materials was classified as semicrystalline or semicrystalline blends (Lukas et al., 2009). The heating rate appeared to affect the rate and extent of co-crystal formation, and solid phases were confirmed by inconsistent temperature X-ray diffraction (XRD).

Another rapid and efficient method to characterize co-crystal is to observe on the crystals morphology by optical microscopy. This feature reveals the outer appearance of crystals as unit cell repetition leads to crystal formations that can be observed by simple hand lens or microscope. Instead of using optical microscopy, for future morphology observation, polarizing optical microscopy, thermal microscopy and electron microscopy can be used. The geometry of crystal shape is almost proverbially anisotropic, in many cases even “faceted”. This implies that some orientation-dependent factor is active during crystal growth. If not, crystal grown under homogenous external condition would be sphere in shape (Van, 1995).

## ***2.8 Model compound and co-crystal former***

Carbamazepine and ibuprofen were chosen as the models drugs in this study. Carbamazepine is a class II compounds which is characterized by a high per-oral dose, in Biopharmaceutical Classification System (BCS) which has low aqueous solubility and high membrane permeability. Dissolution rate limited the bioavailability of such a class II drug (Rinaki et al., 2003). In contrast, ibuprofen is a class II compound with high permeability, has low bioavailability due to its low aqueous solubility in water but very soluble in various organic solvents (Patel et al., 2010).